REMARKS

Claims 3, 4, 7, 8, and 18 are pending and under examination in the subject application. Applicants have not added, cancelled, or amended any claims.

Information Disclosure Statement

The Examiner indicated on page 3 of the July 12, 2011 Office Action that the listing of references in the specification is not a proper information disclosure statement. The Examiner indicated that 37 C.F.R. §1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and M.P.E.P. §609.04(a) states that "the list may not be incorporated into the specification but must be submitted in a separate paper". The Examiner concluded that unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

In response, all of the references listed in the specification of the subject application have previously been disclosed to the U.S. Patent and Trademark Office in Information Disclosure Statements submitted on September 17, 2007, January 22, 2008 or December 4, 2009 in connection with the subject application. In this regard, applicants received with the December 22, 2010 Final Office Action copies of Forms PTO 1449 (Substitute) previously submitted which are initialed by the Examiner. Therefore, applicants understand that the references listed in the specification and listed on the initialed Form PTO 1449 (substitute) have been considered by the Examiner.

Accordingly, applicants request that the Examiner reconsider and withdraw the preceding objection.

Copending Applications

The Examiner indicated on page 3 of the July 12, 2011 Office Action that applicants must bring to the attention of the Examiner information within their knowledge as to other copending U.S. applications which are "material to patentability" of the application in question.

As noted in applicants' responses filed October 15, 2010 and May 13, 2011, applicants understand that the Examiner is already aware of U.S. Patent No. 6,831,073 issued December 14, 2004 on behalf of Michael Lanquetin. This patent was disclosed in the Information Disclosure Statement filed September 17, 2007.

As indicated in applicants' responses filed October 15, 2010 and May 13, 2011, and in order to insure compliance with the duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following copending applications or patents, the claimed subject matter of each of which concerns methods of contraception, not methods of hormonal replacement therapy.

1. U.S. Serial No. 11/649,672, filed January 3, 2007, was disclosed in an Information Disclosure Statement filed September 17, 2007. This application was published as US 2007-0281912 A1 on December 6, 2007 and this publication number was disclosed in an Information Disclosure Statement filed December 4, 2009. On July 10, 2010 U.S. Serial No. 11/649,672 issued as U.S. Patent No. 7,749,987 B2. U.S. Patent No. 7,749,987 B2 was disclosed in the Supplemental Information Disclosure Statement filed October 15, 2010.

2. U.S. Serial No. 12/079,335, filed March 25, 2008, was published as US 2008-0242650 A1 on October 2, 2008. This patent application publication number was disclosed in the Supplemental Information Disclosure Statement filed October 15, 2010.

3. U.S. Patent No. 6,906,049, issued June 14, 2005 in the name of Paris et al., was disclosed in the Information Disclosure Statement filed September 17, 2007.

Accordingly, applicants request that the Examiner reconsider and withdraw the preceding objection.

Specification

On page 3 of the July 12, 2011 Office Action the Examiner indicated that the priority data must be added at the beginning of the specification.

In response, applicants reiterate that the subject application claims priority under 35 U.S.C. §119 of PCT International Application No. PCT/FR99/02588, filed October 25, 1999. 35 U.S.C. §119 does not require or even permit that the specification contain or be amended to contain a specific reference to an application previously filed outside the United States from which priority under 35 U.S.C. §119 is being claimed. In contrast, 35 U.S.C. §120 requires that a U.S. application claiming the benefit of an earlier-filed U.S. application contain or be amended to contain a specific reference to an earlier-filed U.S. application from which benefit is being claimed under 35 U.S.C. §120.

Accordingly, applicants request that the Examiner reconsider and withdraw the preceding objection.

Rejection Under 35 U.S.C. §103(a)

On pages 4 to 10 of the July 12, 2011 Office Action the Examiner rejected claims 3, 4, 7, 8, and 18 under 35 U.S.C. § 103(a) as obvious over Plunkett et al. (U.S. Reissue No. 36,247), Blanc et al. (Clinical Therapeutics, 1998), and Casper (U.S. Patent No. 5,256,421).

The Examiner asserted that Plunkett et al. teaches a pharmaceutical composition for hormonal treatment of menopausal or post-menopausal disorders in a woman, which comprises a dosage unit of a progestogen and a dosage unit of an estrogen for continuous administration wherein the dosage units comprise a progestogen in the range of 0.025 to 30 mg and an estrogen in the range of 0.005 to 2.5 mg together with a pharmaceutically acceptable inert carrier. The Examiner asserted that Plunkett el. teach that the actual unit dosages are selected according to conventionally known methods, e.g., body weight of the patient and biological activity of the hormones, with the ultimate goal of producing the desired result with the minimum quantities of hormones.

The Examiner acknowledged that Plunkett et al. does not disclose nomegestrol acetate.

The Examiner then asserted that Blanc et al. teaches continuous hormone replacement therapy combining nomegestrol acetate and a gel, patch, or oral estrogen in postmenopausal women. The Examiner further asserted that Blanc et al. teaches 2.5 mg/dose of nomegestrol acetate, whereas the presently claimed amount of nomegestrol acetate is 0.625 to 1.25 mg/dose.

The statement of the grounds for rejection does not discuss the disclosure of Casper.

The Examiner asserted that it would have been obvious to one skilled in the art to prepare additional beneficial compounds useful for hormone replacement therapy in menopausal women using minimum quantities of hormones which does not initiate bleeding or increase the risk of endometrial carcinoma. The Examiner asserted that there has been ample motivation provided by the teachings of Plunkett et al. and Blanc et al. to prepare the instant invention in the absence of any criticality or unexpected results. The Examiner asserted that it is not unexpected from Plunkett et al. in view of Blanc et al. that one of ordinary skill in the art would give the minimal effective dose in order to avoid unwanted side effects. The Examiner asserted that those of ordinary skill in the art would have readily optimized effective dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient.

Applicants' Response

In response, applicants respectfully traverse the ground of rejection.

Initially, and as acknowledged by the Examiner, Plunkett et al. does not disclose nomegestrol acetate and therefore cannot disclose an oral dose range of nomegestrol acetate to be administered to an estrogen deficient, menopausal woman. Similarly, Casper does not disclose nomegestrol acetate. Blanc et al. disclose use of nomegestrol acetate at a dose of 2.5 mg/day, which is a dose which does not fall within,

or overlap with, the 0.625 to 1.25 mg dosage range recited in applicants' claimed method.

The Examiner has attempted to remedy this deficiency in the combination of cited references by asserting that "it has been further held that a *prima facie* case of obviousness exists where the claimed ranges and the prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties" and cited *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

In *Titanium Metals*, a copy of which is attached hereto as **Exhibit A**, claims 1-3 which were at issue recited titanium alloy compositions, not a method of use as is the case for applicants' pending claims. See, *Titanium Metals* at 776. The Federal Circuit found clams 1 and 2 anticipated by a single prior art reference. *Id.* at 782. Claim 3, which was dependent upon claim 1, recited a "titanium base alloy as set forth in Claim 1 having 0.8% nickel, 0.3% molybdenum, up to 0.1% maximum iron, balance titanium." *Id.* at 776. The Federal Circuit found that a single prior art reference disclosed titanium alloys having "compositions very close to that of claim 3." *Id.* at 783. Specifically, the composition of one prior art alloy was 0.25% molybdenum and 0.75% nickel, and the composition of a second prior art alloy was 0.31% molybdenum and 0.94% nickel. *Id.* Thus, the percentages of molybdenum and nickel recited by claim 3 were so close to the values in the single prior art reference that the values for molybdenum and nickel recited by claim 3 could be obtained by simply rounding off the values disclosed in the prior art reference. The Federal Circuit concluded that "the proportions are so close that prima facie one skilled in the art would have expected them to have the same properties." *Id.*

In contrast to the situation of *Titanium Metals* where the claims were directed to a composition and the values could be obtained by rounding off values disclosed in the prior art to the nearest tenth of a percent, applicants' claims are directed to a method which differs from the method disclosed in all of the cited references except Plunkett, the obviousness rejection is based on a combination of references, not a single prior art reference, and the dosage of nomegestrol acetate disclosed for a different purpose by Blanc et al., i.e., 2.5 mg, is two (2) to four (4) fold higher than the 0.625 to 1.25 mg dosage range recited in applicants' pending claims. Accordingly, the holding of *Titanium Metals* in inapplicable to the instant claims.

Even if, *arguendo*, there were a basis for a finding of *prima facie* obviousness of applicants' claimed invention from the combination of cited references, applicants have presented evidence of an unexpected result sufficient to rebut any such *prima facie* case of obviousness.

For example, applicants' specification teaches:

> The biopsies of the endometrium examined at the end of the trial showed no proliferative or hyperplastic appearance of the uterine mucosa. The highest percentage of secretory endometria was observed in the women who had received the highest progestative dose; it decreased progressively and in a statistically significant way with the dose. In contrast, the highest percentage of atrophic endometria was found at the lowest progestative dose and this decreased as the dose increased.
>
> These results are <u>unexpected</u> in the sense that they show that low doses of nomegestrol acetate administered in continuous combination with an estrogen are capable of preventing the growth of the uterine mucosa and keeping it in an atrophic condition, whereas, in contrast to higher

> doses, they are insufficient to induce a secretory transformation of the endometrium.
>
> Thus, this trial reveals a surprising decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect, when it is administered in continuous combination with estrogens.

Subject specification, page 21, line 31 to page 22, line 13, emphasis added.

See also, January 26, 2006 Declaration Under 37 C.F.R. § 1.132 of Dr. Jean-Louis Thomas, of record. For the Examiner's convenience, a copy is attached hereto as **Exhibit B**. In particular, see page 5, paragraphs 6-10, which discuss applicants' data which is presented in the subject specification:

> Moreover, Table 2 on page 24 of the specification of the present application shows the results of biopsies of the endometrium of women treated with the combination of the invention. A comparison is made between the combination containing 2.5 mg of nomegestrol acetate (i.e. the dose disclosed in Blanc et al.) and combinations containing lower doses of nomegestrol acetate as presently claimed.
>
> It can be seen that the number of atrophic endometria significantly increased at the doses of 1.25 mg (a 25 % increase) and 0.625 mg (a 138 % increase) of nomegestrol acetate, as compared to the dose of 2.5 mg taught by Blanc et al.
>
> This means that the endometrium is protected because when an endometrium is atrophic then no hyperplasia (excessive growth of tissue) occurs.
>
> At the same time, the low doses of nomegestrol acetate are insufficient to induce a secretory transformation of the endometrium (as can be seen from table 2, the number of secretory endometrium significantly decreases with the dose).

> Accordingly, it is thus surprising and unexpected that at doses which are insufficient to induce a secretoty transformation of the endometrium, nomegestrol acetate, when administered with an estrogen, nevertheless exerts a protecting effect on the endometrium by keeping it in atrophic state.

A combination of Plunkett et al., Blanc et al. and Casper does not teach the surprising effect on endometrial atrophy which results from administration of nomegesrol acetate at the low oral dosage range recited in applicants' claimed method.

The July 12, 2011 Office Action addresses the Declaration of Dr. Thomas on pages 11-12, but does not identify any specific prior art reference which teaches the unexpected result discovered by applicants, i.e. the decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect when administered at the low oral dosage range recited by applicants' claimed method, or explain why the result is not unexpected.

Accordingly, the evidence of record rebuts any *prima facie* case of obviousness presented by the combination of cited prior art.

In view of the preceding remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 3, 4, 7, 8, 18 under 35 U.S.C. §103(a).

Rejections Under 35 U.S.C. §112, second paragraph

On page 10 of the July 12, 2011 Office Action, the Examiner rejected claims 3, 4, 7, 8, and 18 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The

Examiner asserted that the meaning of "to effect the hormonal replacement therapy" in claim 18 is unclear. The Examiner requested that applicants explain the meaning of the phrase.

In response, applicants respectfully traverse the rejection. As an initial point applicants note that the Examiner has misquoted the claim which reads "to effect hormonal replacement therapy." The word "the" does not appear before the word "hormonal."

As a second point applicants note that the phrase "to effect hormonal replacement therapy..." means that the administration of the free estradiol or estradiol ester and nomegestrol acetate in the recited dose ranges "effect," i.e., accomplishes the hormonal replacement therapy recited in the preamble of the claim. See, definition of "effect" (transitive verb) from Merriam Webster online dictionary, a copy of which is attached hereto as **Exhibit C**.

In view of the preceding comments applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, second paragraph.

Conclusion

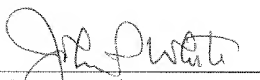
For the reasons set forth, applicants maintain that the grounds of the Examiner's objections and rejections have been overcome and respectfully request that the Examiner reconsider and withdraw these grounds of objection and rejection and allow pending claims 3, 4, 7, 8 and 18.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned

attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $150.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
30 Rockefeller Plaza
20th Floor
New York, New York 10112
(212) 278-0400

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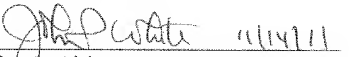

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John P. White
Reg. No. 28,678

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(Cite as: 778 F.2d 775)

▷

United States Court of Appeals,
Federal Circuit.
TITANIUM METALS CORPORATION OF AMERICA, Appellee,
v.
Donald W. BANNER, Commissioner of Patents and Trademarks, Appellant.

Appeal No. 85–1452.
Nov. 7, 1985.

Civil action was brought against Commissioner of Patents and Trademarks authorizing Commissioner to issue patent for titanium alloy. The United States District Court for the District of Columbia, John Garrett Penn, J., authorized Commissioner to issue patent, and Commissioner appealed. The Court of Appeals for the Federal Circuit, Rich, Circuit Judge, held that patent was improperly issued.

Reversed.

West Headnotes

[1] Patents 291 ⇐68

291 Patents
291II Patentability
291II(D) Anticipation
291k67 Prior Description in Printed Publication
291k68 k. Requisites of publication. Most Cited Cases

Anticipation under 35 U.S.C.A. § 102 can be found only when reference discloses exactly what is claimed, and when there are differences between reference disclosure and claim, rejection must be based on statute [35 U.S.C.A. § 103] which takes differences into account.

[2] Patents 291 ⇐324.55(2)

291 Patents
291XII Infringement
291XII(B) Actions
291k324 Appeal
291k324.55 Questions of Fact, Verdicts, and Findings
291k324.55(2) k. Clearly erroneous findings. Most Cited Cases

Patent claim interpretation is a question of law free from clearly erroneous standard of review.

[3] Patents 291 ⇐70

291 Patents
291II Patentability
291II(D) Anticipation
291k67 Prior Description in Printed Publication
291k70 k. Operation and effect. Most Cited Cases

Patent was improperly issued for claims 1 and 2 of patent application for titanium alloy since claims were anticipated under 35 U.S.C.A. § 102 by Russian article which admittedly disclosed alloy on which those claims read.

[4] Patents 291 ⇐16.34

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.34 k. Metallurgy and mining. Most Cited Cases

Specific alloy of claim 3 of patent application for titanium alloy was obvious from known alloys and therefore invalid for obviousness. 35 U.S.C.A. § 103.

*775 Fred E. McKelvey, Deputy Sol., U.S. Patent and Trademark Office of Arlington, Va., argued for appellant. With him on the brief were Joseph F. Nakamura, Sol. and Henry W. Tarring, II, Associate Sol., Washington, DC.

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(Cite as: 778 F.2d 775)

David C. Bruening, Webb, Burden, Robinson & Webb, P.A., of Pittsburgh, Pa., argued for appellee. With him on the brief was Richard L. Byrne.

***776** Before RICH, Circuit Judge, NICHOLS, Senior Circuit Judge, and NEWMAN, Circuit Judge.

RICH, Circuit Judge.

This appeal is from an Order of the United States District Court for the District of Columbia in a civil action brought pursuant to 35 U.S.C. § 145 against Donald W. Banner as Commissioner of Patents and Trademarks[FN1] authorizing the Commissioner to issue to appellee a patent containing claims 1, 2, and 3 of patent application serial No. 598,935 for "TITANIUM ALLOY." The Commissioner has appealed. We reverse.

FN1. After suit was brought and before entry of said Order, Commissioner Gerald J. Mossinghoff, Banner's successor in office, was substituted as defendant. He has, in turn, been succeeded by Donald J. Quigg, but no formal substitution of Quigg has been made.

Background

The inventors, Loren C. Covington and Howard R. Palmer, employees of appellee to whom they have assigned their invention and the application thereon, filed an application on March 29, 1974, serial No. 455,964, to patent an alloy they developed. The application involved on this appeal is a continuation-in-part thereof, filed July 25, 1975, containing the three claims on appeal. The alloy is made primarily of titanium (Ti) and contains small amounts of nickel (Ni) and molybdenum (Mo) as alloying ingredients to give the alloy certain desirable properties, particularly corrosion resistance in hot brine solutions, while retaining workability so that articles such as tubing can be fabricated from it by rolling, welding and other techniques. The inventors apparently also found that iron content should be limited, iron being an undesired impurity rather than an alloying ingredient. They determined the permissible ranges of the components, above and below which the desired properties were not obtained. A precise definition of the invention sought to be patented is found in the claims, set forth below, claim 3 representing the preferred composition, it being understood, however, that no iron at all would be even more preferred.

1. A titanium base alloy consisting essentially by weight of about 0.6% to 0.9% nickel, 0.2% to 0.4% molybdenum, up to 0.2% maximum iron, balance titanium, said alloy being characterized by good corrosion resistance in hot brine environments.

2. A titanium base alloy as set forth in Claim 1 having up to 0.1% iron, balance titanium.

3. A titanium base alloy as set forth in Claim 1 having 0.8% nickel, 0.3% molybdenum, up to 0.1% maximum iron, balance titanium.

The examiner's final rejection, repeated in his Answer on appeal to the Patent and Trademark Office (PTO) Board of Appeals (board), was on the grounds that claims 1 and 2 are anticipated (fully met) by, and claim 3 would have been obvious from, an article by Kalabukhova and Mikheyew, *Investigation of the Mechanical Properties of Ti-Mo-Ni Alloys,* Russian Metallurgy (Metally) No. 3, pages 130–133 (1970) (in the court below and hereinafter called "the Russian article") under 35 U.S.C. §§ 102 and 103, respectively. The board affirmed the examiner's rejection. However, it mistakenly proceeded on the assumption that all three claims had been rejected as anticipated under § 102 by the Russian article and ignored the obviousness rejection. On this appeal the PTO says it does not pursue the § 103 rejection further. Appellee proceeds on the basis that only the § 102 rejection is before us.

Both the examiner and the board had before them as evidence three affidavits by Rosenberg, Palmer, and Hall and a declaration by Minkler, by which they were not persuaded of patentability.

The Russian article is short (3 pages), highly technical, and contains 10 graphs as part of the discussion. As its title indicates, it relates to ternary Ti-Mo-Ni alloys, the subject of the application at bar. The examiner and the board both found that it would disclose to one skilled in the art an ***777** alloy on which at least claims 1 and 2 read, so that those claims would not be allowable under the statute because of lack of novelty of their subject matter. Since the article does not specifically disclose such an alloy *in words,* a little thinking is required about what it would disclose to one knowledgeable about Ti-Ni-Mo alloys. The PTO did that thinking as follows:

> Figure Ic [a graph] shows data for the ternary titanium alloy which contains Mo and Ni in the ratio of 1:3. Amongst the actual points on the graph is one at 1% Mo + Ni. At this point, the amounts of Mo and Ni would be 0.25% and 0.75% respectively. A similar point appears on the graph shown in Figure 2 of the article.
>
> ....
>
> Appellants do not deny that the data points are disclosed in the reference. In fact, the Hall affidavit indicates at least two specific points (at 1% and 1.25% Mo + Ni) which would represent a description of alloys falling within the scope of the instant claims.

On that basis, the board found that the claimed alloys were not new, because they were disclosed in the prior art. It having been argued that the Russian article contains no disclosure of corrosion-resistant *properties* of any of the alloys, the board held:

> The fact that a particular property or the end use for this alloy as contemplated by appellants was not recognized in the article is of no consequence.

It therefore held the Russian article to be an anticipation, noting that although the article does not discuss corrosion resistance, it does disclose other properties such as strength and ductility. The PTO further points out that the authors of the reference must have made the alloys to obtain the data points.

Being dissatisfied with the decision of the board, Titanium Metals Corporation of America, as assignee of the Covington and Palmer application, then brought an action in the District Court for the District of Columbia against the Commissioner pursuant to 35 U.S.C. § 145, its complaint alleging that the board's decision "was erroneous and contrary to law," and making profert of a certified copy of the application and all papers in the file thereof, together with a copy of the Russian article which was the sole basis of the PTO refusal to allow the claims. It prayed that the court adjudge it entitled to a patent containing claims 1–3 and authorize the Commissioner to grant such a patent. The Commissioner filed an answer denying that the applicants were the first inventors of the alloys claimed or entitled to a patent, alleging that the claims are not patentable under the law, and making profert of the Examiner's Answer, the Board of Appeals' decision, and the prior art reference.

The case came on for trial on January 24, 1980, before the Honorable John G. Penn and was concluded in two and a half hours. The testimony of one witness was heard by the court, Dr. James C. Williams, professor at Carnegie-Mellon University in Pittsburgh and an expert in titanium metallurgy. His testimony was about equally divided between direct and cross examination.

At the conclusion of the plaintiff's case, the following exchange took place between the judge and the Associate Solicitor for the PTO:

> THE COURT: All right. Mr. Tarring?
>
> MR. TARRING: Your Honor, generally the position of the Patent Office is we rely on the position of the tribunals below, the examiner and the Board of Appeals and their decisions are both present in the exhibit which I submitted earlier. I was not quite sure whether you would prefer that we have a post-trial brief in the matter. If that's your preference we could do that or I could make an argument on the basis of the law right now. I don't know what your preference would be. Otherwise, I'm not going to call any witnesses.
>
> THE COURT: You are not going to what?
>
> MR. TARRING: I have no intention of calling any witnesses so it's really a matter of argument at this point, I think.
>
> *778 THE COURT: Of course, I have received your pre-trial briefs.

After further discussion, it was settled that both parties would file further briefs after the hearing transcript had been prepared. They were filed in April and May, 1980. On November 16, 1984, the District Court entered the Order appealed from followed on November 28 by a supporting memorandum opinion. January 10, 1985, the PTO filed its Notice of Appeal. This court has heard oral argument and received briefs.

The District Court Opinion

The trial court's memorandum opinion [FN2] having been published, we shall merely outline its contents.

FN2. Reported sub nom. *Titanium Metals Corporation of America v. Mossinghoff*, 603 F.Supp. 87, 225 USPQ 673 (D.D.C.1984).

After stating the nature of the action and the relief sought, Part I is a summarization of the contents of the patent specification, a statement of the issues, and of the PTO rejection which is stated both correctly as the examiner made it and incorrectly as the board assumed it to be. Part II is a statement of the District of Columbia Circuit Court of Appeals' attitude toward plaintiff's burden on review of the PTO board decisions in § 145 actions, namely, that it is a "heavy burden," "great weight" being given to the PTO decision because of its "expertise," a "thorough conviction" that it erred being required, as well as a lack of a "rational basis for its conclusions." In Part III is a brief discussion of "anticipation" under § 102 with citation of two cases from our predecessor Court of Customs and Patent Appeals, *In re Wilder*, 429 F.2d 447, 57 C.C.P.A. 1314, 166 UPSQ 545 (1970), and *In re LeGrice*, 301 F.2d 929, 49 C.C.P.A. 1124, 133 USPQ 365 (1962), with emphasis placed on their holdings that an anticipatory reference must be an "enabling" reference, the implication being that the Russian article perhaps does not enable one to know all the things that the plaintiff's inventors disclosed in their application, such as the range limits of the alloying ingredients Mo and Ni and the corrosion resistance. The court then states that after considering all of the affidavit and declaration evidence which was before the PTO, it still lacked the necessary "thorough conviction" required to overturn the PTO decision even though, left to its own judgment of the evidence, it would be willing to do so. It then reviewed the evidence of Dr. Williams taken before it. Dr. Williams was qualified as an expert in titanium metallurgy but not in patent law. The questions he was asked, however, pertained to the interpretation of patent claims, as quoted in the court's opinion. The court was of the view that his testimony "fully supports the arguments made by the plaintiff in this case" and found it "to be very persuasive." The court then concluded that claims 1–3 were not anticipated and that claim 3 was wrongly rejected as directed to obvious subject matter. In the court's view, Dr. Williams' testimony tipped the scales in favor of issuing a patent.

OPINION

I. Jurisdiction

This suit was brought in the district court pursuant to 35 U.S.C. § 145. Our jurisdiction rests on 28 U.S.C. § 1295(a)(4)(C) which provides as follows:

§ 1295. *Jurisdiction of the United States Court of Appeals for the Federal Circuit*

(a) The United States Court of Appeals for the Federal Circuit shall have exclusive jurisdiction—

....

(4) of an appeal from a decision of—

....

(C) a district court to which a case was directed pursuant to section 145 or 146 of title 35;

....

This case having been directed to the District Court for the District of Columbia by § 145, this court's jurisdiction is *exclusive* of the Court of Appeals for the District of ***779** Columbia and is therefore governed by the precedents of this court and its predecessor courts. *See South Corporation v. United States*, 690 F.2d 1368, 215 USPQ 657 (Fed.Cir.1982).

Strange as it may seem to any district judge not to be governed by the precedents of his own Court of Appeals, that is the situation created by Congress in the Federal Courts Improvement Act of 1982, § 402 of Pub.L. 97–164, Apr. 2, 1982, 96 Stat. 37, effective Oct. 1, 1982, in the interest of promoting a uniform patent law by having only one Court of Appeals deciding questions of patent law, whether review be of decisions of the Patent and Trademark Office or of district court judgments in cases arising under the patent laws of the United States. *Cf.* § 1295(a)(1). We do not fault the district judge, however, for having stated the precedents of his own circuit in this § 145 case because this is one of the first occasions we have had to review a judgment in such a case. Nor do we

need to determine whether we should apply those precedents here.

2. The rejections under review

Tracing the PTO rejections under review below, we encounter confusion. Although we are reviewing the judgment (in the form of an order) of the district court,[FN3] the effect of that order is to hold that the PTO's rejections of claims 1–3 were in error. The actual holding of the district court was:

> FN3. The Order entered Nov. 16, 1984, after preliminary recitations, reads as follows:
>
> > ORDERED that the Commissioner of Patents and Trademarks is authorized to issue to plaintiff, Titanium Metals Corporation of America, as assignee and owner of application Serial No. 598,935, United States Letters Patent on Titanium Alloy including Claims Nos. 1, 2 and 3 in due form as prescribed by the Patent Laws of the United States.
> >
> > The ultimate issue actually before us is *whether the patent laws permit* the Commissioner to issue such a patent.

The Court concludes that Claims 1, 2 and 3 should not have been rejected on the basis of anticipation pursuant to 35 U.S.C. § 102. Moreover, the Court concludes that Claim 3 should not have been rejected as being obvious pursuant to 35 U.S.C. § 103.

Thus, the Court finds as a fact and concludes as a matter of law that the decision of the Board of Appeals was in error. The testimony of Dr. Williams, which remains uncontradicted, adds sufficient weight to the plaintiff's side to tip the scales and, in the Court's view, to result in clear and convincing evidence that the application should not have been rejected.

Thus, the court deemed all three claims to have been rejected for anticipation under § 102. The examiner never so rejected claim 3. The board opinion, as above noted, erroneously assumed that he had, never gave any special or separate attention to claim 3, never discussed obviousness or § 103, and concluded its opinion with the words "The decision of the examiner is affirmed." The board made no new rejection, as it might have done, under 37 C.F.R. § 196(b). Under these circumstances, we shall assume that the board intended to, and did, affirm *only* the rejection that the examiner had made, as we have stated at the beginning, and that the only rejection outstanding against claim 3 is for obviousness under § 103.

The district court assumed there were *two* outstanding rejections against claim 3. We have reduced it to one.

The appellee, because it quite evidently suits its argument best, has preferred to ignore the § 103 rejection of claim 3, but we do not because it exists in the official record.

[1] The PTO brief says the Commissioner "is not pursuing" the § 103 rejection in this court, but it is before us whether or not pursued by the PTO. The PTO Solicitor developed a new theory in his brief, never propounded by either the examiner or the board, to support a § 102 rejection of claim 3 on the Russian article,[FN4] but that ***780** was clearly beyond his province and we disregard it as amounting to a new ground of rejection. We also disregard it as contrary to many holdings of this court and its predecessors that anticipation under § 102 can be found only when the reference discloses exactly what is claimed and that where there are differences between the reference disclosure and the claim, the rejection must be based on § 103 which takes differences into account. D. Chisum, *Patents* § 3.02.

> FN4. Resting on the fact that the Russian Article discloses an alloy containing 0.75% Ni and 0.25% Mo, the Solicitor's argument is as follows:
>
> > Moreover, this alloy falls within the scope of claim 3, which specifies 0.8% nickel, 0.3% molybdenum, up to 0.1% iron and balance titanium. Inasmuch as this claim specifies the content of nickel and molybdenum to a tenth of a percent, the claim, given the broadest reasonable interpretation, would cover alloys the amounts of whose contents would correspond to the claim language when expressed in tenths

> of a percent. Following the usual convention of rounding off hundredths to tenths by increasing the tenths digit by one when the hundredths digit to be dropped is five or greater, the alloy of the Russian article, expressed in tenths of a percent, would contain 0.8% nickel, 0.3% molybdenum and balance titanium, corresponding to the alloy specified in tenths of a percent in claim 3.

We have undertaken to settle the question whether we are dealing with one ground of rejection or two for the further reason that the standard of review of this court may vary in accordance with what the rejection is and whether it is considered to be a finding of fact or a conclusion of law. We have held that anticipation is a finding of fact, reviewable under the "clearly erroneous" standard, *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 225 USPQ 634 (Fed.Cir.1985), and that obviousness is a conclusion of law not subject to that restraint, but is freely reviewable. *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 1344, 220 USPQ 777, 782 (Fed.Cir.1984). That may make a difference in our review.

3. The merits

Finding, as we do, that claim 3 was never purposefully rejected under § 102, both the board and the district court being confused about that fact, we are left with the propriety of the rejection of claims 1 and 2 under § 102 and the rejection of claim 3 under § 103, both rejections having been held by the district court to have been erroneous. That necessarily follows from the court's conclusion "that the Claims are patentable." We find that conclusion contrary to statutory law and will deal with the two grounds of rejection separately.

A. Anticipation, § 102

From consideration of the trial court's memorandum opinion, we are unable to determine whether it erred because of miscontruction of the claims, misreading of what the reference discloses, lack of proper advice on the requirements of the patent statute respecting patentability, or the technical legal meaning of "anticipation," a term which some courts have erroneously used from time to time.

We are left in no doubt that the court was impressed by the totality of the evidence that the applicants for patent had discovered or invented and disclosed knowledge which is not to be found in the reference, nor do we have any doubt about that ourselves. But those facts are beside the point. The patent law imposes certain fundamental conditions for patentability, paramount among them being the condition that what is sought to be patented, as determined by the claims, be new. The basic provision of Title 35 applicable here is § 101, providing in relevant part: "Whoever invents or discovers any *new* ... composition of matter, or any *new* ... improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." (Emphasis ours.) The title of the application here involved is "Titanium Alloy," a composition of matter. Surprisingly, in all of the evidence, nobody discussed the key issue of whether the alloy was new, which is the essence of the anticipation issue, including the expert Dr. Williams. Plaintiff's counsel, bringing Dr. Williams' testimony to its climax, after he had explained the nature of the ingredients, the alloys made therefrom, and their superior corrosion resistance in hot brine, *781 etc., repetitively asked him such questions as "Does the [Russian] article *direct you* as one skilled in the art to a titanium alloy having nickel present in an amount between .6 and .9 percent molybdenum in an amount between .2 and .4 percent?" (emphasis ours) followed by "Is there anything mentioned in the article about corrosion resistance?" Of course, the answers were emphatically negative. But this and like testimony does not deal with the critical question: do claims 1 and 2, to which the questions obviously relate, *read on or encompass* an alloy which was already known by reason of the disclosure of the Russian article?

Section 102, the usual basis for rejection for lack of novelty or anticipation, lays down certain principles for determining the novelty required by § 101, among which are the provisions in § 102(a) and (b) that the claimed invention has *not* been "described in a printed publication in this or a foreign country," either (a) before the invention by the applicant or (b) more than one year before the application date to which he is entitled (strictly a "loss of right" provision similar to novelty). Either provision applies in this case, the Russian article having a date some 5 years prior to the filing date and its status as "prior art" not being questioned. The PTO was never specific as to what part of § 102 applies, merely rejecting on § 102. The question, therefore, is whether claims 1 and 2 encompass and, if allowed, would enable plain-

tiff-appellee to exclude others from making, using, or selling an alloy *described* in the Russian article. *See* 35 U.S.C. § 154. *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 218 USPQ 781 (Fed.Cir.1983).

To answer the question we need only turn to the affidavit of James A. Hall, a metallurgist employed by appellee's TIMET Division, who undertook to analyze the Russian article disclosure by calculating the ingredient percentages shown in the graph data points, which he presented in tabular form. There are 15 items in his table. The second item shows a titanium base alloy containing 0.25% by weight Mo and 0.75% Ni and this is squarely within the ranges of 0.2–0.4% Mo and 0.6–0.9% Ni of claims 1 and 2. As to that disclosed alloy of the prior art, there can be no question that claims 1 and 2 read on it and would be infringed by anyone making, using, or selling it. Therefore, *the statute prohibits* a patent containing them. This seems to be a case either of not adequately considering the novelty requirement of the statute, the true meaning of the correlative term "anticipation," or the meaning of the claims.

By reason of the court's quotations from cases holding that a reference is not an anticipation which does not enable one skilled in the art to practice the claimed invention, it appears that the trial court thought there was some deficiency in the Russian article on that score. Enablement in this case involves only being able to make the alloy, given the ingredients and their proportions without more. The evidence here, however, clearly answers that question in two ways. Appellee's own patent application does not undertake to tell anyone how to make the alloy it describes and seeks to patent. It assumes that those skilled in the art would know how. Secondly, appellee's expert, Dr. Williams, testified on cross examination that given the alloy information in the Russian article, he would know how to prepare the alloys "by at least three techniques." Enablement is not a problem in this case.

As we read the situation, the court was misled by the arguments and evidence to the effect that the inventors here found out and disclosed in their application many things that one cannot learn from reading the Russian article and that this was sufficient in law to justify granting them a patent for their contributions—such things as what good corrosion resistance the claimed alloys have against hot brine, which possibly was not known, and the range limits of the Ni and Mo content, outside of which that resistance diminishes, which are teachings of very useful information. These things the applicants teach the art and the Russian article does not. Indeed, appellee's counsel argued in his opening***782** statement to the trial court that the PTO's refusal of a patent was "directly contrary to the requirement of Article I, Section 8, of the Constitution," which authorizes Congress to create a patent law. But throughout the trial counsel never came to grips with the real issues: (1) what do the claims cover and (2) is what they cover new? Under the laws Congress wrote, they must be considered. Congress has not seen fit to permit the patenting of an old alloy, known to others through a printed publication, by one who has discovered its corrosion resistance or other useful properties, or has found out to what extent one can modify the composition of the alloy without losing such properties.

[2] It is also possible that the trial court did not properly interpret the claims and took them to be directed only to the applicants' discoveries about the properties of the alloys instead of to the alloys themselves, as they are, possibly because of the phrase at the end of claim 1, "characterized by good corrosion resistance in hot brine environments," which applies to the other two dependent claims also. No light is shed by its opinion on what the court thought the claims mean as the opinion does not construe the claims. Until it has been definitely determined what subject matter is being claimed, it is not known what it is that the PTO held to be unpatentable. Claim interpretation, which is the logical starting point of the analysis, is a question of law free from the clearly erroneous standard of review. *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed.Cir.1983). It is the correct and necessary construction of all three claims that they simply define titanium base *alloys*. Claims 1 and 2 state certain narrow limits within which the alloying ingredients, Mo and Ni, are present and necessarily cover a number of alloys. Claim 3 is specific to a single alloy. This said, it is immaterial, on the issue of their novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties.

The trial court and appellee have relied on *In re Wilder*, supra, but they have both failed to note those portions of that opinion most relevant to the present

case. The issue there, as here, was anticipation of certain claims. Wilder argued "that even though there may be a technical anticipation, the discovery of the new property and the recitation of this property in the claims 'lends patentable novelty' to the claims." The court answered:

> However, recitation, in a claim to a composition, of a particular property said to be possessed by the recited composition, be that property newly-discovered or not, does not necessarily change the scope of the subject matter otherwise defined by that claim. [429 F.2d at 450, 57 C.C.P.A. 1314, 166 UPSQ at 548.]

The court in that case also said:

> [W]e start with the proposition that claims cannot be obtained to that which is not new. This was the basis of the holding in *In re Thuau* [135 F.2d 344, 30 C.C.P.A. 979, 57 USPQ 324 (CCPA 1943)]. It was the law then, is now and will be until Congress decrees otherwise. [Id.]

It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is "anticipated" if *one* of them is in the prior art. *In re Petering*, 301 F.2d 676, 682, 49 C.C.P.A. 993, 1001, 133 USPQ 275, 280 (1962).

[3] For all of the foregoing reasons, the court below committed clear error and legal error in authorizing the issuance of a patent on claims 1 and 2 since, properly construed, they are anticipated under § 102 by the Russian article which admittedly discloses an alloy on which these claims read.

B. Obviousness, § 103

[4] Little more need be said in support of the examiner's rejection of claim 3, affirmed by the board, on the ground that its more specific subject matter would have been obvious at the time the invention was ***783** made from the knowledge disclosed in the reference.

As admitted by appellee's affidavit evidence from James A. Hall, the Russian article discloses two alloys having compositions very close to that of claim 3, which is 0.3% Mo and 0.8% Ni, balance titanium. The two alloys in the prior art have 0.25% Mo—0.75% Ni and 0.31% Mo—0.94% Ni, respectively. The proportions are so close that prima facie one skilled in the art would have expected them to have the same properties. Appellee produced no evidence to rebut that prima facie case. The specific alloy of claim 3 must therefore be considered to have been obvious from known alloys.

Conclusion

For the foregoing reasons, the decision and order of the district court holding that claims 1, 2, and 3 are directed to patentable subject matter and authorizing the issuance of a patent thereon were clearly erroneous and are *reversed.*

REVERSED.

C.A.Fed. (Dist.Col.), 1985.
Titanium Metals Corp. of America v. Banner
778 F.2d 775, 227 U.S.P.Q. 773

END OF DOCUMENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application: Jacques PARIS et al.
Serial No 09/423,109 — Art Unit: 1616
Filed on: October 29, 1999 — Examiner: Qazi

For: New hormonal composition and its use.

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

The undersigned, Jean-Louis THOMAS, of France, declares as follows:

1. I am a Medical Doctor (MD) and a Pharmacist holding such degree from the University of Nancy (France).

I have fulfilled the following functions:

1969-1972:	Pharmacist Resident, Nancy hospitals
1973-1975:	Consulting Pharmacist, Nancy hospitals
1975-1976:	Medical Resident, Hôpital des Armées, Nancy
1976-1980:	Medical Resident, Nancy hospitals
1980-1984:	Assistant Resident, Centre Hospitalier Universitaire (CHU), Nancy
1984-1985:	Senior Consultant-Assistant professor, CHU, Nancy
1985-1987:	Senior Consultant, Nancy hospitals
Since 1985:	Director of the clinical Research and Development Department, Théramex Laboratory, Paris
Since 1988:	Senior Consultant, Paris hospitals (Department of Endocrinology, Diabetology and Nutrition, CHU Henri-Mondor, Créteil)

I devoted many years of my professional life in the field of Endocrinology and Clinical Pharmacology.

I am the applicant of several publications, many of them on the use of hormones in women.

I direct a team that develops hormones for use in contraception and menopause.

2. I am a co-inventor of the captioned application.

3. I have read the prior art documents cited against the present application and I am of the opinion that they do not suggest the claimed method of treating estrogenic deficiencies in women.

4. I present hereafter the arguments which sustain my opinion.

4.1. PLUNKETT (US Re 36,247) fails to disclose Nomegestrol acetate as progestin and the properties thereof.

Plunkett disclosed a method for treatment of menopausal disorders comprising continuous or intermittent administration of an estrogen / progestin combination, claiming that all estrogens and all progestins can be used indiscriminately, providing that equivalent doses are administered. Nevertheless, the Applicant has the opinion that the Plunkett's patent cannot be opposed to the present application because they did not claim the use of NOMAC and because the choice of active doses cannot be based on a rule of "equivalence". Anybody skilled in the art knows that each progestin has its own pharmacological profile and cannot automatically be replaced by any other available progestin and that the rule of equivalence is not in accordance with scientific knowledge.

- *NOMAC brings original properties*

  NOMAC is not comparable to other progestins; it has an original pharmacological profile which is not shared with any other available progestin. In summary, contrary to 19 nor-testosterone derivates, it does not bring any androgenic and estrogenic residual activity and, contrary to 17α-hydroxyprogesterone derivatives, it has a strong antigonadotropic activity (Table 1).

Table 1: **NOMAC pharmacological profile**

NOMAC	OTHER PROGESTINS	
	progesterone derivatives	19-nor testosterone derivatives
Strong progestagen activity	Strong progestagen activity, except progesterone	
without androgenic residual effects without estrogenic residual effects without gluco-corticoid residual effects without deleterious metabolic effects	with or without androgenic residual effects without estrogenic residual effects with or without gluco-corticoid residual effects with or without deleterious metabolic effects	with androgenic residual effects with estrogenic residual effects with gluco-corticoid residual effects with deleterious metabolic effects
Strong antigonadotropic activity	Slight antigonadotropic activity	Strong antigonadotropic activity

- *The "equivalence" rule has no scientific support*

The choice of active doses cannot be based on the "equivalence" rule for different reasons:

1. as described above, the profile of progestins is very different in term of pharmacological activity and adverse effects so that one progestin cannot automatically replace another for a given therapeutic use;

2. active doses must be chosen case by case from clinical data and/or opinion of anybody skilled in the art because:

   a. there is no agreement about active doses of a given progestin; minimum dose and maximal doses are very different between patents claiming the same therapeutic use; an example is given in Table 2: considering WO 95/1/17194, EP 025607 A1 and Plunkett's patent, minimal and maximal active doses of levonorgestrel, desogestrel and 3-ketodesogestrel are very different.

Table 2: Differences in active doses (µg/day) in different patents claming for the same therapeutic use

Progestin	Patent	Dose (µg/day)	
		Mini	Maxi
levonorgestrel	WO 95/17194	60	125
	EP 025607 A1	25	100
	PLUNKETT	25	75
gestodene	WO 95/17194	50	75
	EP 025607 A1	10	70
desogestrel	WO 95/17194	60	150
	EP 025607 A1	25	100
3-ketodesogestrel	WO 95/17194	60	150
	EP 025607 A1	25	100
norethisterone	WO 95/17194	350	750
	EP 025607 A1	85	350
	PLUNKETT	150	1000

   b. active doses of progestins are depending on pharmacological and/or clinical targets; consequently, it is impossible to propose equivalent doses without indicating the target. Considering HRT, two targets can be chosen, either histological effects on the endometrium or effects on menstruation. Data presented in Table 3 clearly show that doses claimed in the Plunkett's patent are very different from values reported in papers from Neumann and Kuhl: for these two well-known specialists of progestins, active doses of levonorgestrel, norgestrel, norethisterone, norethisterone acetate, norethynodrel and lynestrenol on endometrium and menstruation are much higher than doses claimed by Plunkett using his equivalence rule (Table 3).

Table 3: **Published active doses of progestins depending on clinical efficacy targets**

Progestin	Plunkett's patent		Neumann's paper		Kuhl's paper
	Mini	Maxi	Endometrium transformation	Withdrawal bleeding delay	Endometrium transformation
levonorgestrel	25	75			400
norgestrel	50	150	1200	2000	
norethisterone	100	1000	12500	5000	10000
norethisterone acetate	100	10000	4500		
medroxyprogesterone acetate	1000	15000	5500	25000	
norethynodrel	2000	8000	10000	7500	
allylestrenol	1000	10000	1750		
lynestrenol	1000	20000	5000		
cyproterone acetate	100	10000	1000		2000

In grey, progestins for which active dose calculated using the equivalence principle are much lower that active doses published by Neumann and Ku

In conclusion, the range of active doses of each progestin must be chosen case by case from clinical data and/or the expertise of anybody skilled in the art and cannot derive from a standard equivalence ratio as proposed by Plunkett.

- *Progestins continuously given with an estrogen induce an endometrial atrophy.*

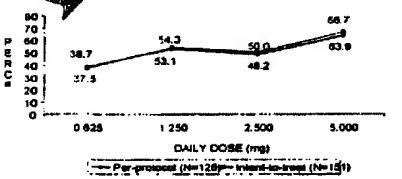
After the issue of the Plunkett's patent, Nomegestrol acetate was shown to have a different effect on endometrium (Fig 1); this effect is characterized by a dissociation between anti-estrogenic and progestagen activity: at low doses, the anti-estrogenic effect is predominant and endometrium is atrophic; at high doses, the progestagen effect is predominant and the endometrium is secretory. Unexpectedly, even with high nomegestrol acetate doses, a large majority of women are amenohrreic (Fig 1). This is a characteristic of nomegestrol acetate, never described for other progestins, which can bring clinical advantages, especially in term of acceptability of treatment and consequently compliance, due to an increase of the percentage of no-bleeding pattern.

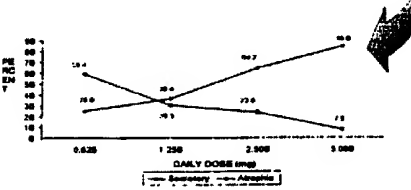
Figure 1 : Endometrial effects of E2/nomegestrol acetate continuous combination

Clinical examples

151 postmenopausal women (treated for 6 months)

Dose E2V mg - NOMAC mg	2.0 0.625	2.0 1.25	2.0 2.5	2.0 5.0
Number of patients	37	37	38	38
Amenorrhea (%)	38.7	54.3	50.0	68.7
Secretory endometrium (%)	25.0	38.4	64.7	88.8
Atrophic endometrium (%)	59.4	30.3	23.5	7.5





4.2. The Blanc et al. reference discloses continuous hormone replacement therapy for menopause combining oral 2.5 mg/day nomegestrol acetate and either percutaneous 17β-estradiol gel (1.5 mg/day), transdermal 17β-estradiol patch (50 µg/day) or oral estradiol valerate (2 mg/day).

According to the results discussed on pages 905-906, the amenorrhea rate (or cycles with no bleeding) was 60 % when oral nomegestrol acetate was combined with oral estradiol valerate, as compared to 78 % when oral nomegestrol acetate was combined with percutaneous estradiol.

There is no suggestion whatever in Blanc et al. to lower the dose of nomegestrol acetate with a view towards correcting estrogen deficiencies or preventing osteoporosis, and then, one of ordinary skill in the art would select neither the regimen when both the nomegestrol and the estrogen are administered orally, nor the range of doses proposed in this present application.

In fact, Blanc et al. teaches that the rate of amenorrhea achieved with continuous combined HRT for menopause is an important factor in patient compliance (page 909, left column, emphasis added).

Since according to Blanc the rate of amenorrhea is higher when nomegestrol acetate is combined with percutaneous estradiol (as discussed above), those skilled in the art seeking to improve the rate of amenorrhea and hence patient compliance would have been deterred from using an oral estrogen in combination with oral nomegestrol acetate.

Moreover, Table 2 on page 24 of the specification of the present application shows the results of biopsies of the endometrium of women treated with the combination of the invention. A comparison is made between the combination containing 2.5 mg of nomegestrol acetate (i.e. the dose disclosed in Blanc et al.) and combinations containing lower doses of nomegestrol acetate as presently claimed.

It can be seen that the number of atrophic endometria significantly increased at the doses of 1.25 mg (a 25 % increase) and 0.625 mg (a 138 % increase) of nomegestrol acetate, as compared to the dose of 2.5 mg taught by Blanc et al.

This means that the endometrium is protected because when an endometrium is atrophic then no hyperplasia (excessive growth of tissue) occurs.

At the same time, the low doses of nomegestrol acetate are insufficient to induce a secretory transformation of the endometrium (as can be seen from table 2, the number of secretory endometrium significantly decreases with the dose).

Accordingly, it is thus surprising and unexpected that at doses which are insufficient to induce a secretory transformation of the endometrium, nomegestrol acetate, when administered with an estrogen, nevertheless exerts a protecting effect on the endometrium by keeping it in atrophic state.

Such results certainly cannot be deducted from the teachings of Plunkett et al. which does not disclose nomegestrol acetate at all, or Blanc et al. which uses higher dose of nomegetrol acetate.

The skilled man would not have been motivated to use a progestin and an estrogen continuously as taught by Plunkett and to use nomegestrol acetate as progestin because Blanc et al. does not provide any incentive to do so. In addition, the effects of nomegestrol acetate on the endometrium are surprising and unexpected when taken in the light of the cited prior art.

5. Furthermore, the following examples carried out under my supervision confirm that the hormonal combination of the invention is useful for correcting estrogenic deficiencies in women and in preventing osteoporosis.

Example 1

In a double-blind multicenter placebo-controlled study, the effect of two estradiol (E2) /nomegestrol acetate (NOMAC) continuous combinations (0.5 mg E2/0.625 mg NOMAC and 1 mg E2/1.25 mg NOMAC) on symptoms related to estrogen deficiency were tested in 114 postmenopausal women.

The women were treated for 3 months and were evaluated at baseline, after 6 weeks and at the end of treatment.

The following table shows the total number of hot flushes recorded by the women within the 7 days before the evaluations.

Treatment	Baseline	6 weeks	3 months	p Value
E2 0.5 mg / NOMAC 0.625 mg	24.1 (36)	3.4 (38)	1.9 (35)	< 0.0001
E2 1 mg / NOMAC 1.25 mg	11.2 (38)	0.5 (40)	0.3 (37)	< 0.0001
Placebo	12.4 (39)	10.2 (36)	8.8 (36)	0.3186

(n) = number of women at each evaluation

The number of hot flushes did not change significantly in the placebo group, but significantly decreases in women treated with the E2/NOMAC combinations of the invention.

Example 2

In a double placebo-controlled study, the effect of two estradiol (E2) /nomegestrol acetate (NOMAC) continuous combinations (0.5 mg E2/0.625 mg NOMAC and 1 mg E2/1.25 mg NOMAC) on blood and urinary type 1-collagen C-telopeptides (CTX) were evaluated in postmenopausal women.

CTX is a bone resorption biological parameter which increases in women with risk of osteoporosis.

The following tables show the plasma and urinary CTX values observed at baseline, after 6 weeks and 3 months of treatment.

Plasma CTX

Treatment	Baseline	6 weeks	3 months	p Value
E2 0.5 mg / NOMAC 0.625 mg	0.5 (38)	0.4 (36)	0.3 (35)	< 0.0001
E2 1 mg / NOMAC 1.25 mg	0.5 (41)	0.3 (40)	0.3 (38)	< 0.0001
Placebo	0.5 (41)	0.5 (40)	0.6 (38)	0.2790

(n) = number of women at each evaluation

Urinary CTX/creatinine ratio

Treatment	Baseline	6 weeks	3 months	p Value
E2 0.5 mg / NOMAC 0.625 mg	285.5 (34)	180.8 (36)	184.0 (35)	< 0.0001
E2 1 mg / NOMAC 1.25 mg	281.9 (40)	155.0 (40)	141.4 (37)	< 0.0001
Placebo	312.8 (41)	319.9 (40)	325.7 (36)	0.5271

(n) = number of women at each evaluation

The CTX values were similar at baseline in the 3 treatment groups, but significantly decreased during treatment with the two E2/NOMAC combinations, while they increased in the placebo group.

These results show that the E2/NOMAC combinations of the invention were able to decrease bone resorption and then to prevent osteoporosis.

* * *

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 26th day of January 2006

Jean-Louis THOMAS

Definition of EFFECT

transitive verb

1 : to cause to come into being

2 **a** : to bring about often by surmounting obstacles : ACCOMPLISH <*effect* a settlement of a dispute>

b : to put into operation <the duty of the legislature to *effect* the will of the citizens>

See effect defined for English-language learners »

Usage Discussion of EFFECT

Effect and *affect* are often confused because of their similar spelling and pronunciation. The verb ²*affect* usually has to do with pretense <she *affected* a cheery disposition despite feeling down>. The more common ³*affect* denotes having an effect or influence <the weather *affected* everyone's mood>. The verb *effect* goes beyond mere influence; it refers to actual achievement of a final result <the new administration hopes to *effect* a peace settlement>. The uncommon noun *affect*, which has a meaning relating to psychology, is also sometimes mistakenly used for the very common *effect*. In ordinary use, the noun you will want is *effect* <waiting for the new law to take *effect*> <the weather had an *effect* on everyone's mood>.

Examples of EFFECT

They are trying to *effect* a settlement of the dispute.

The duty of the legislature is to *effect* the will of the people.

When, at last, rescue is at hand, Jewitt has no hesitation in lying to his old friend and master, Maquinna, in order to *effect* his escape, although he does persuade the captain of the brig Lydia not to kill the chief. —Carolyn Kizer, *New York Times Book Review*, 21 Feb. 1988

[+] more

Origin of EFFECT

(see ¹EFFECT)

First Known Use: 1533

Applicants: J. Paris et al.
U.S. Serial No. : 09/423,109
Filed : October 29, 1999
Exhibit C